Effects of Halogen Bonding on ^{13}C NMR Shifts of Iodotolan

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Approved By

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ACKNOWLEDGEMENTS

This thesis could not have been completed without the help of my advisor, Dr. Daniell Mattern. I am also grateful for the help received from graduate student, Trey Vaughan, and my fellow undergraduate researchers especially Kailin Blanton, Tarrah Frederick, and Henry Nguyen.

ABSTRACT

Halogen bonding is the ability of heavier halogens to have noncovalent interactions similar to hydrogen bonding. By mixing two compounds that should halogen bond together and analyzing this mixture with carbon NMR spectroscopy, we attempted to test the strength and extent of halogen bonding in 4-iodotolan. After observing the changes in the 4-iodotolans chemical shifts, the halogen bond appears to be too weak to affect the chemical shifts in a substantial manner; however, the C-I bonded carbon shows a slight but consistent increase in its shift which could be an avenue for future research.

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Introduction

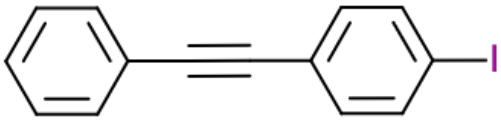

Figure 1.1: 4-iodotolan

Halogens are typically known as electronegative atoms making them very powerful nucleophiles with high electron density; however, this electron density is not spread equally throughout the atom when it is covalently bonded. This separation creates two different regions in the atom, one with high electron density and another with much lower electron density with a potentially postive electrostatic region. The positive region is known as the sigma hole, as it reflects the electron distribution associated with the sigma molecular orbital that covalently bonds it to the other atom[1]. This sigma hole is also shown to be more positive in heavier halogens due to the larger proton count. With this positive region, a halogen atom can act as an electrophile, or a Lewis acid, instead of the expected nucleophile. A halogen interacting with other atoms as an electrophile is termed a halogen bond (denoted XB). For this paper, we have attempted to quantify the extent of halogen bonding using chemical shifts in a ^{13}C NMR spectrum. Using 4-iodotolan as the halogenated compound, three different electron donors of different concentrations were added to form halogen bonds with the iodine atom of 4-iodotolan.

Chapter 2

The Sonogashira Coupling Reaction

The 4-iodotolan used in this experiment was created using a Sonogashira coupling reaction. The Sonogashira reaction allows for the formation of new C-C bonds between terminal alkynes and aryl or vinyl halides. A palladium catalyst, a copper cocatalyst, and an amine base are the typical reaction conditions for a Sonogashira coupling to occur. These catalysts are, however, water sensitive, and the Sonogashira is thus performed under anhydrous conditions. A number of newer procedures have been able to find new methods for performing a Sonogashira coupling without anhydrous restrictions, and one of these methods was attempted to create the 4-iodotolan (Procedure 1 and 2). Unfortunately, this method was unsuccessful in creating the 4-iodotolan, so a more traditional procedure was used (Procedure 3). Using 1,4-diiodobenzene (an aryl halide) and phenylacetylene (a terminal alkyne) as reactants led to a successful synthesis of 4-iodotolan; however, these reagents may also result in a different molecule since 1,4-diiodobenzene possesses two sites for a new C-C bond. Being a symmetrical molecule, either site will lead to the 4-iodotolan, but after synthesis, the 4-iodotolan still contains an aryl halide and may undergo a Sonogashira coupling again. What prevents this double coupling is the different activation energies for the diiodobenzene and the

4-iodotolan. The 4-iodotolan is already quite a large molecule and would possess a much higher activation energy than the diiodobenzene with its smaller size and two activation sites.

Sonogashira coupling begins with the palladium catalyst (species A) performing an oxidative addition with the aryl halide resulting in species B. Simultaneously, the copper catalyst replaces the methine group in the presence of base forming species F. The two catalyst bonded species perform a transmetallation step with the halide being replaced by the acetylene group forming species C. The palladium catalyst is then expelled in a reductive elimination step forming the product.

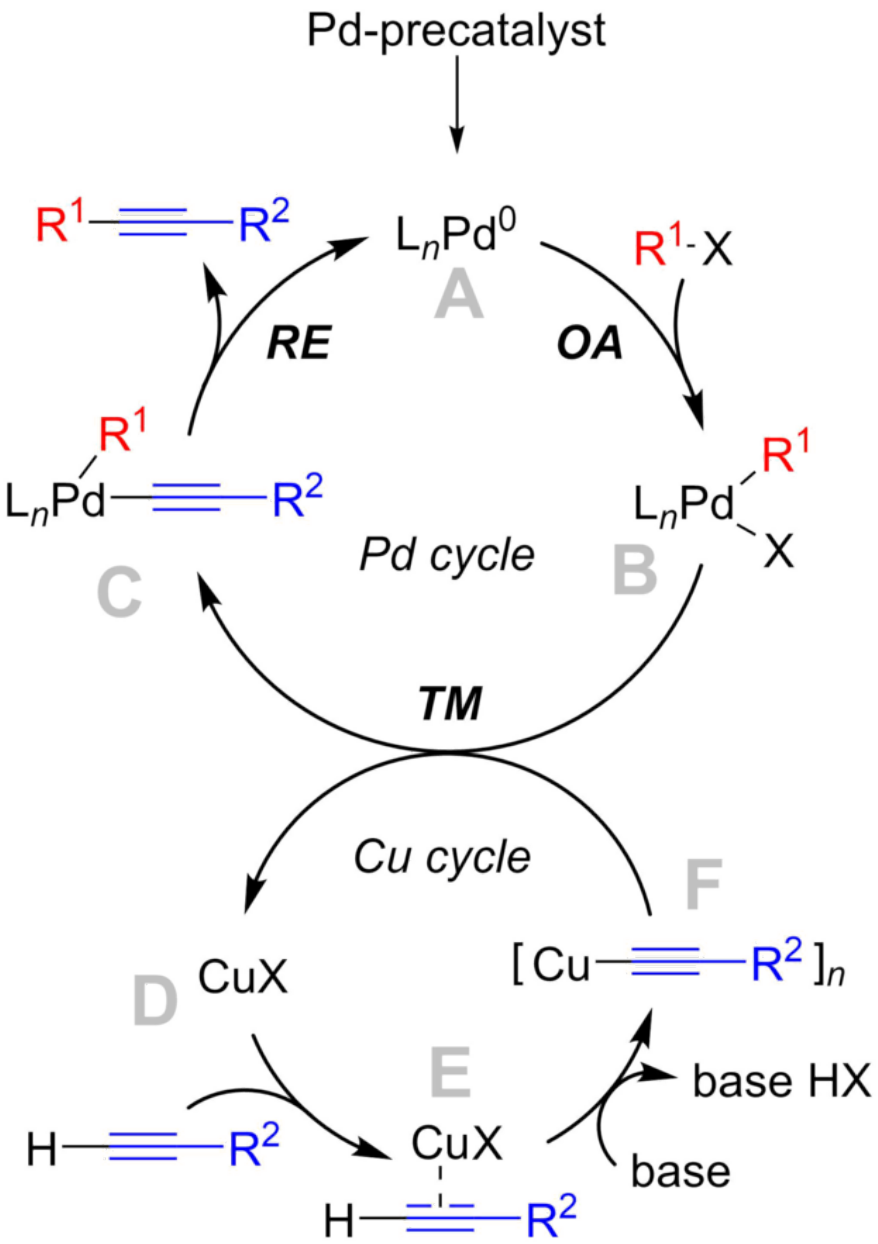

Figure 2.1: Sonogashira Coupling Mechanism [2]

Chapter 3

Attempted Purification

Following the Sonogashira coupling reaction, the remaining diiodobenzene and phenylacetylene were separated with column chromatography; however, the product had low solubility in hexane, so it could not be introduced onto the column in solution. By using a dry-loading technique (Procedure 7.3), a column was successfully performed; however, only the diiodobenzene impurity was removed. Phenylacetylene and the 4-iodotolan possess a very similar Rf value which prevents an effective separation with a column. To remedy this, a selective hydration reaction was performed on the phenylacetylene-4-iodotolan mixture using anhydrous $FeCl_3$ (Procedure 7.4). By estimating the quantity of phenylacetylene to be about 25% using Carbon NMR intesity values, an equivalent amount of $FeCl_3$ and 3 equivalents of H_2O were used to convert the phenylacetylene into a ketone [3]. This ketone differed enough in Rf value to allow an effective column separation. After this second column, the phenylacetylene contamination was reduced to <10%. While a <5% contamination would have been preferred, the experiment was continued to NMR analysis due to time constraints.

Chapter 4

Examining the Shifts of Iodotolan

4.1 Process

Three different lone pair donors were added to 4-iodotolan to observe how halogen bonding would affect its carbon NMR. These three lone pair donors were pyridine, triphenylphosphine, and 3-propanethiol. Each donor was added in a 1:5 donor:4-iodotolan molar ratio to a separate NMR tube of 30 mg of 4-iodotolan dissolved in chloroform-d and a carbon NMR was taken. After each NMR, more of the donor was added to the tube in order to take additional NMRs at 5 other molar ratios, 1:2, 1:1, 2:1, 5:1, and 10:1. All NMRs were taken within a few days to ensure the instrument's calibration remained as constant as possible.

4.2 Results

For each NMR, the chemical shifts of the 4-iodotolan were recorded and compared to the shifts of the pure 4-iodotolan. Shifts are measured in ppm. All graphs are calibrated to the TMS peak at 0 ppm. Peaks are numbered by chemical shift from greatest to smallest. Carbon peaks 4 and 5 are both located at around 128 ppm, the same location as contaminant phenylacetylene's largest peak. These two peaks cannot be distinguished from the phenylacetylene peak, so are absent from the data set. All raw NMR graphs can be found in Appendix A.

Peak 1	Peak 2	Peak 3	Peak 6	Peak 7	Peak 8	Peak 9	Peak 10
137.51	133.08	131.59	122.9	122.79	94.1	90.79	88.44

Table 4.1: NMR Shifts of 4-Iodotolan in $CDCl_3$

	Peak 1	Peak 2	Peak 3	Peak 6	Peak 7	Peak 8	Peak 9	Peak 10
1:5 (least)	0.01	0.01	0.01	0.01	0.02	-0.01	-0.01	0
1:2	0.01	0.01	0.01	0.01	0.02	-0.01	0	0
1:1	0.01	0.01	0.01	0.01	0.02	-0.01	0	-0.01
2:1	0.01	0.01	0.01	0.01	0.02	0	0	-0.01
5:1	0	0.01	0.01	0.02	0.02	0	0	-0.01
10:1 (most)	0	0	-0.01	0.02	0.03	0.03	0	-0.02

Table 4.2: NMR Shift Changes with Additions of 3-propanethiol

	Peak 1	Peak 2	Peak 3	Peak 6	Peak 7	Peak 8	Peak 9	Peak 10
1:5 (least)	0	0	0	0	0	0	0	0
1:2	0.01	0	0	0	0	0	0	0
1:1	0	0.01	0.01	0	0.01	0	0	0
2:1	0	0	0	0	0.01	0	0.01	0
5:1	0	0	0	0	0.01	0.02	0.03	0.01
10:1 (most)	0	-0.01	-0.01	0	0	0.06	0.06	0.03

Table 4.3: NMR Shift Changes with Additions of Pyridine

	Peak 1	Peak 2	Peak 3	Peak 6	Peak 7	Peak 8	Peak 9	Peak 10
1:5 (least)	0	0	0	0	0.01	0	-0.01	0
1:2	0	0	0	0	0.01	0	-0.01	0
1:1	0	0	0	0	0	0.01	-0.01	0
2:1	-0.03	-0.02	-0.03	-0.02	-0.03	-0.01	-0.01	-0.01
5:1	-0.05	-0.04	-0.04	-0.04	-0.05	0.02	0	0
10:1 (most)	-0.11	-0.11	-0.08	-0.08	-0.12	0.07	0.01	-0.04

Table 4.4: NMR Shift Changes with Additions of Triphenylphosphine

	CDCl3
1:5	-0.03
1:2	-0.02
1:1	-0.01
2:1	0.02
5:1	0.13
10:1	0.31

Table 4.5: Movement of $CDCl_3$ in Pyridine

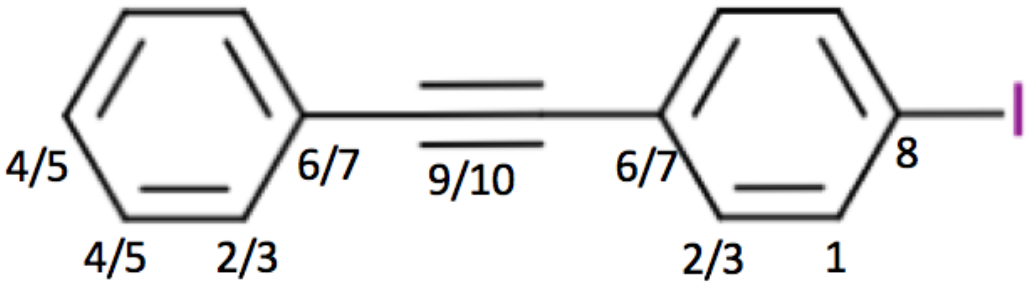

Figure 4.1: Peak Assignments

Chapter 5

Conclusion

When examining the NMR data, peak 8 must be analyzed first, as it is the carbon possessing the C-I bond and should be the most impacted by halogen bonding. For all three donors, peak 8 stays relatively constant except at the very high molar ratios 5:1 and 10:1. At these high concentrations, peak 8 increases slightly for every donor meaning carbon 8 is experiencing some kind of deshielding either from the removal of electron density, magnetic induction, or some other phenomenon to increase the carbon's perceived magnetic field. The halogen bond is expected to increase the electron density, as the lone pair donor aligns and gets closer to the iodotolan. One possible explanation is the lone pair donor pulls some of the electron density on the iodine towards itself and away from the carbon leading to decreased electron density.

Looking at the other peaks shows no uniform movement for all three lone pair donor systems. Interestingly, there is a significant amount of shielding occurring to the benzyllic carbons with the addition of triphenylphosphine; however, this is probably attributable to some unique quality of triphenylphosphine and not the halogen bonding effect.

One other interesting movement comes from the chloroform-d peak in the pyridine system (Table 4.5). Large ratios of pyridine caused the chloroform-d peak to increase in chemical shift much more than any of the iodotolan peaks.

If the chloroform-d peak had been used for calibration instead of TMS in the case of pyridine, a substantial deshielding effect would have been seen in the iodotolan. This large shift is possibly due to a solvent effect that only pyridine has on chloroform. Tests have been done that conclude many solvents including chloroform have an effect on pyridine's chemical shift[4], so it is not unlikely that the reverse is also true and pyridine affects chloroform's shift. This uncertainty prevents us from concluding that the halogen bonding causes a deshielding of iodotolan.

Overall, there is not enough consistency in the NMR data to confirm that halogen bonding is powerful enough to affect the carbon NMR shifts of the iodotolan. There are some signs of a weak shifting in the C-I bonding carbon which has the potential for further research. Finally, a similar set of experiments could be done with bromotolan or chlorotolan, which are expected to have much weaker sigma holes, as negative controls.

Chapter 6

Future Work

The main uncertainty of the experiment is the inability to determine whether the halogen bonding is what is affecting the slight changes in chemical shift. Since the observed change is very small, this experiment could be repeated a number of times to acquire average shift changes ensuring consistency. Also in future experiments, it would be beneficial if a more pure iodotolan could be used, as it is possible the phenylacetylene pollutant is affecting the halogen bonding system. This removal would also allow the inclusion of peaks 4 and 5 into the data set. Additionally, additional halogen bonding compounds other than the three employed in this experiment could be used.

Chapter 7

Procedures

7.1 Copper-free Sonogashira Synthesis of 4-iodotolan

Add 1mmol of diidobenzene and 4mmol of phenylacetylene to flask containing 0.5mmol of tetrabutyl ammonium bromide, 10% mol of $NiCl_2 \cdot 6\,H_2O$, 2 mmol of NaOH, and 2 mL of ethylene glycol. Heat in oil bath at 120°C while stirring for 3 hours. Monitor reaction completion with TLC. After completion, cool mixture to room temperature and extract with diethyl ether. Purify by column chromatography over silica gel using n-hexane/ethyl acetate (5:1) as eluent.[6]

7.2 Palladium Sonogashira Synthesis of 4-iodotolan

Add 2.5g of diiodobenzene and 0.33mL of phenylacetylene to round bottom flask containing 105 mg of bis(triphenylphosphine) palladium(II) dichloride catalyst, 30 mg of copper(II) iodide catalyst, 5 mL of diisopropylamine, and 45 mL of toluene. Stir without heating overnight under nitrogen. Atmospheric conditions will deactivate catalysts. Extract with dichloromethane, and wash with saturated NH_4Cl and brine. Dry with magnesium sulfate. After filtration, evaporate remaining solvents. Purify with column chromatography. [5]

7.3 Column Chromatography Purification by Dry-Loading

Crude product of Procedure 3 dissolved in dichloromethane. 10x mass of product of silica gel added to sample and mixed gently. Solvent was evaporated using rotary evaporator. Sample-infused silica gel added to top of prepared column using hexane as eluent.

7.4 Hydration of Phenylacetylene

1 equivalent of anhydrous $FeCl_3$, 1 equivalent of phenylacetylene, and 3 equivalents of H20 were dissolved in dichloromethane. Solution was stirred at room temperature for 24 hours. Product was extracted with H_2O-Et_2O 1:1 mixture. [3]

7.5 Carbon Shift Testing

30mg of 4-iodotolan was added to a dry NMR tube and dissolved in $CDCl_3$. Lone pair donor was added to reach a 1:5 molar ratio of lone pair to 4-iodotolan, and a 256 scan ^{13}C NMR was taken. After scan, more lone pair donor was added to reach new 1:2 molar ratio. Process repeated for 1:1, 2:1, 5:1, and 10:1. For solid donors, a scale was used to determine mass. For liquid donors, a 10 micro-liter pipette was used instead.

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[4] Mantsch, H. H., and Smith, I. C. A study of solvent effects on the ^{13}C nuclear magnetic resonance spectra of cholesterol, pyridine, and uridinel. *Canadian Journal of Chemistry 51*, 9 (1973), 1384–1391.

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[6] Wang, S., et al. Cui-catalyzed suzuki coupling reaction of organoboronic acids with alkynyl bromides. *Tetrahedron 67*, 26 (2011), 4800–4806.

Chapter 8

Appendix

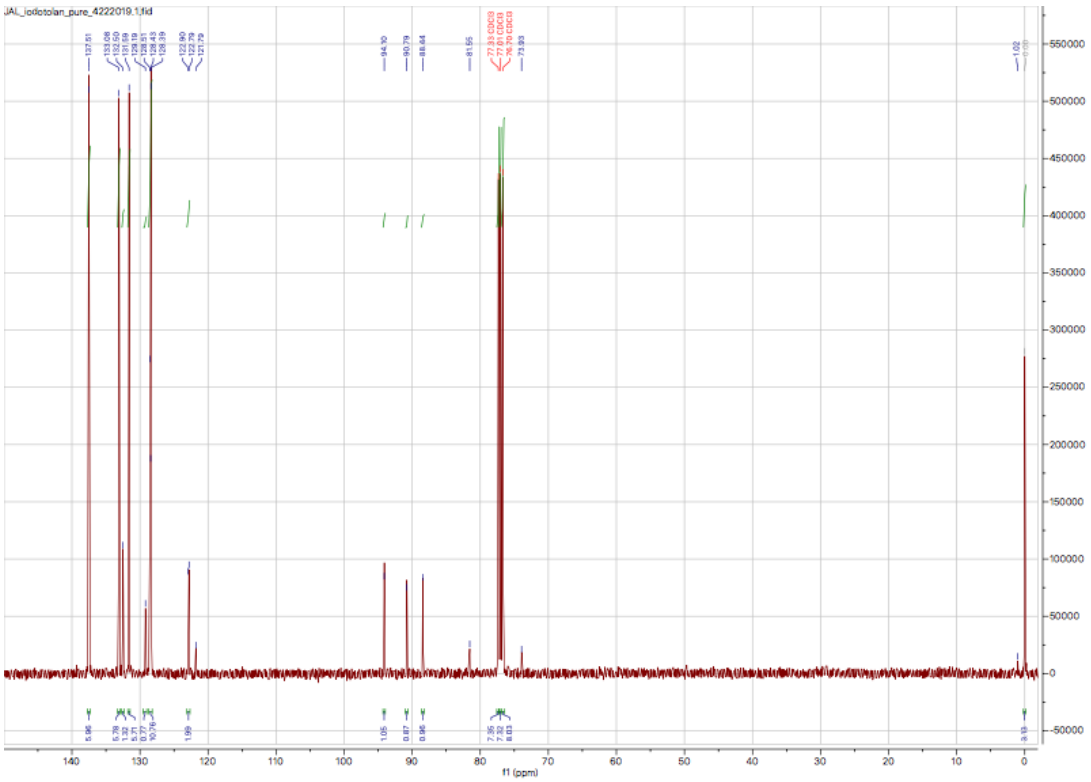

Figure 8.1: Iodotolan Base Shifts

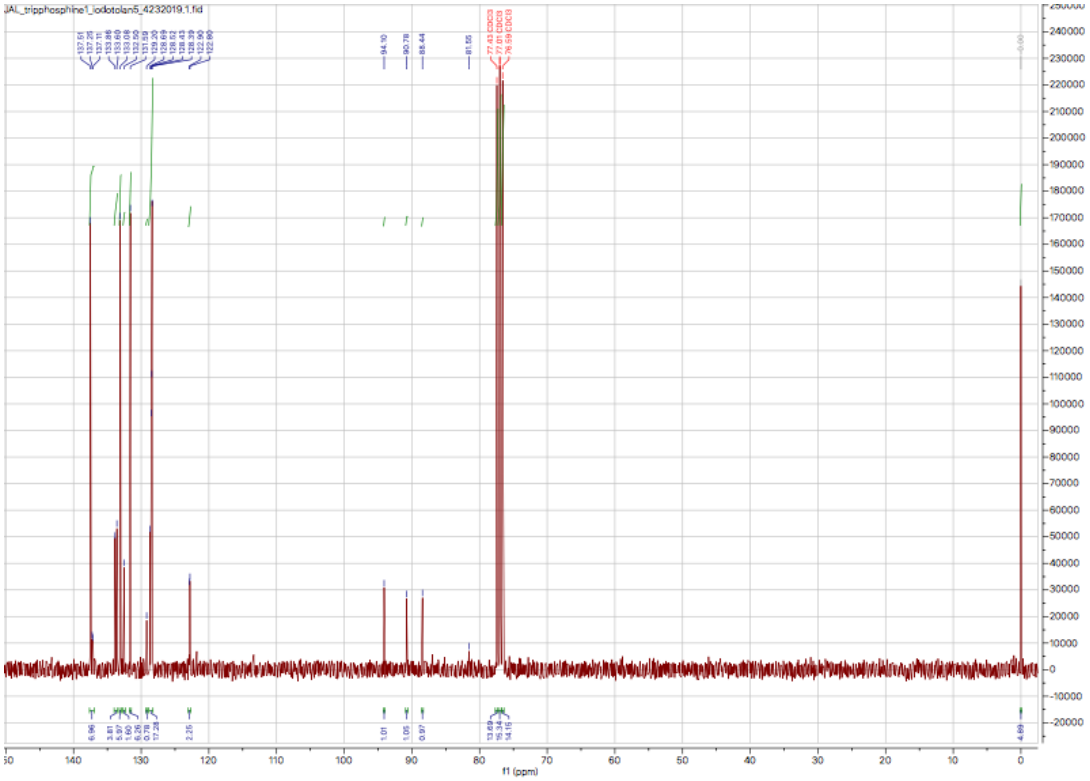

Figure 8.2: Triphenylphosphine 1:5

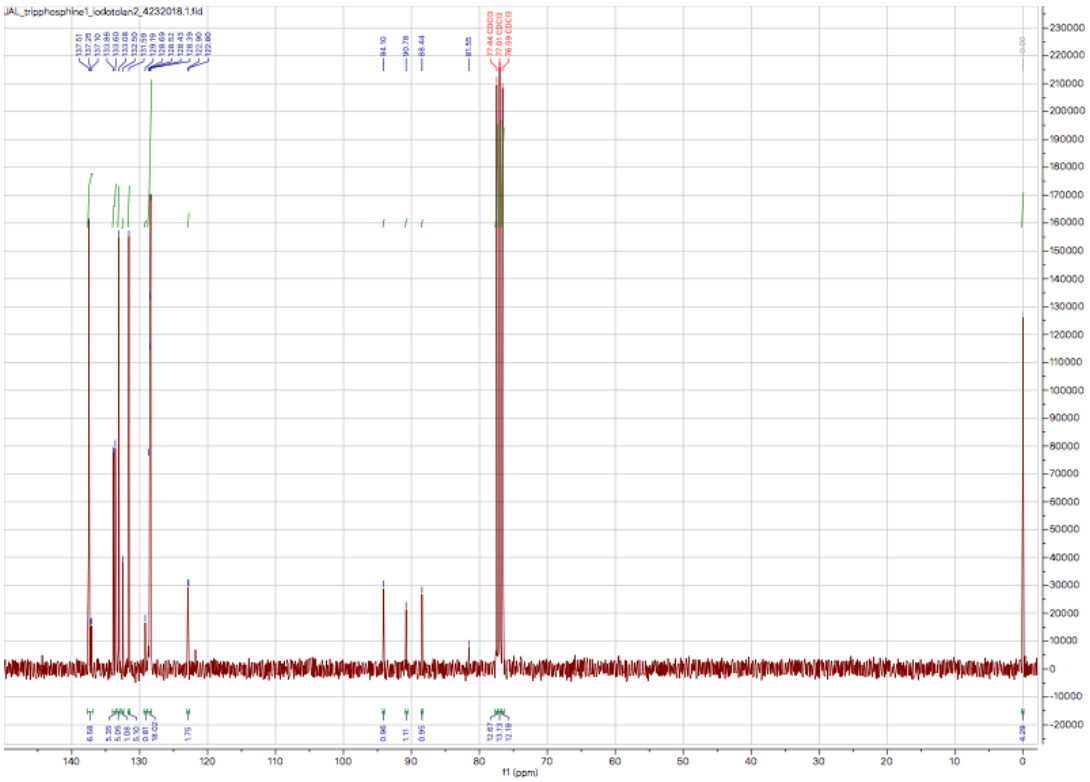

Figure 8.3: Triphenylphosphine 1:2

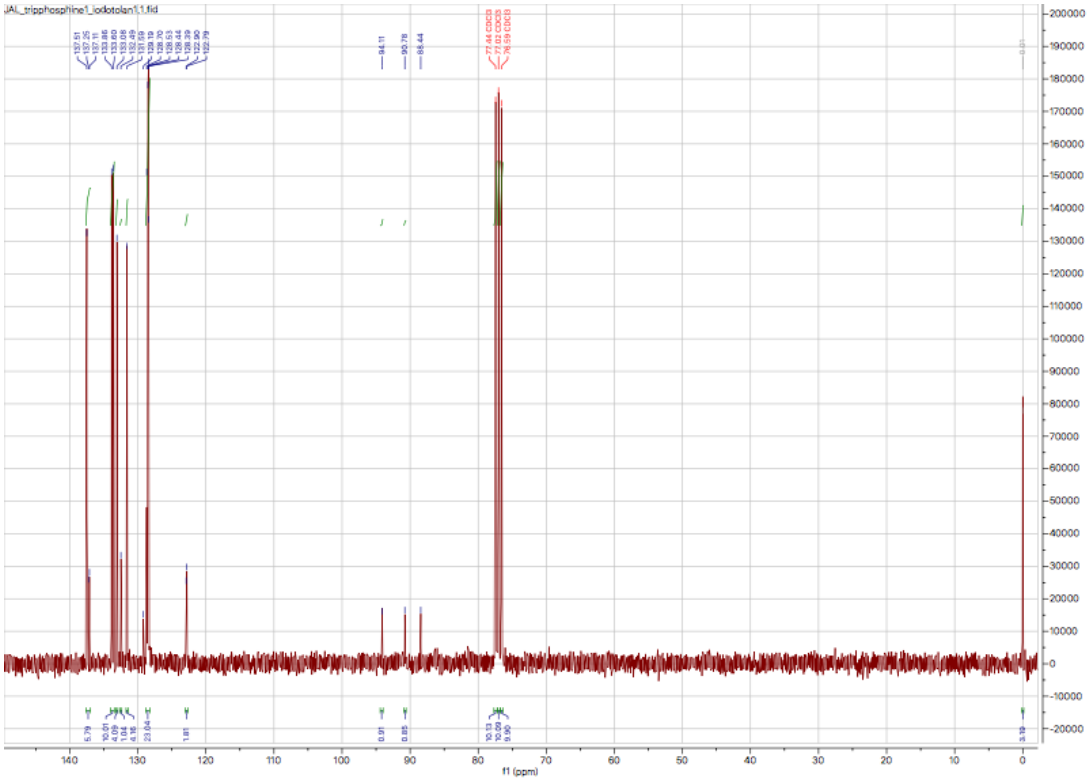

Figure 8.4: Triphenylphosphine 1:1

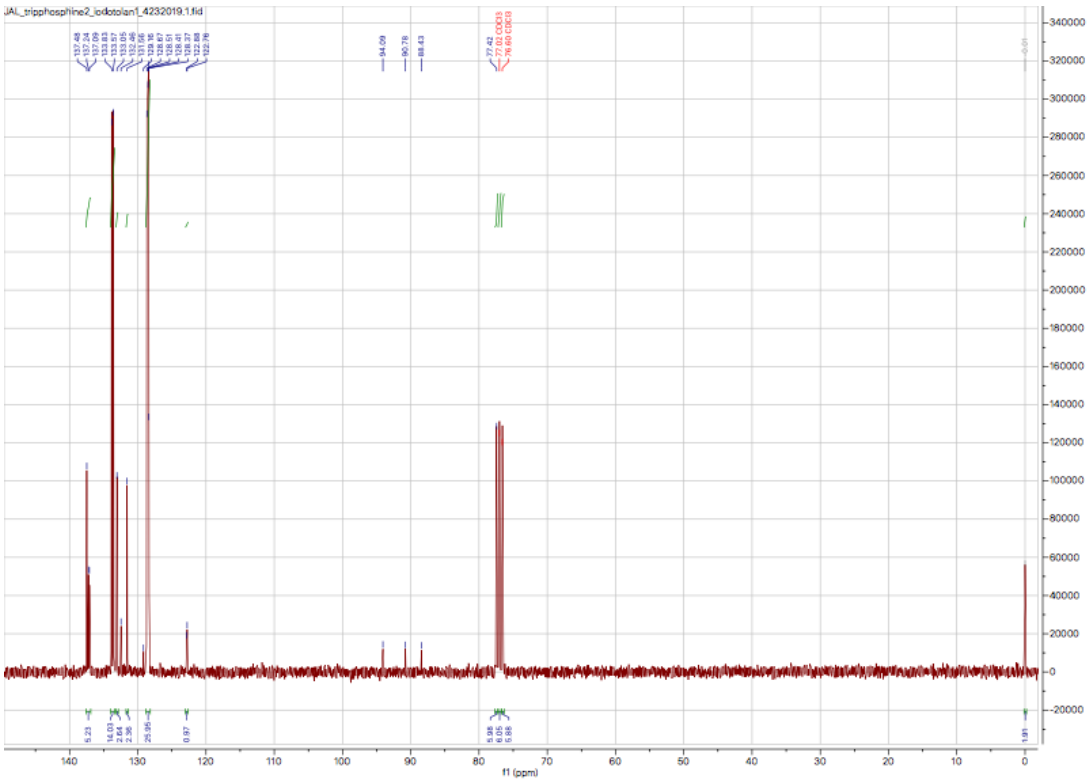

Figure 8.5: Triphenylphosphine 2:1

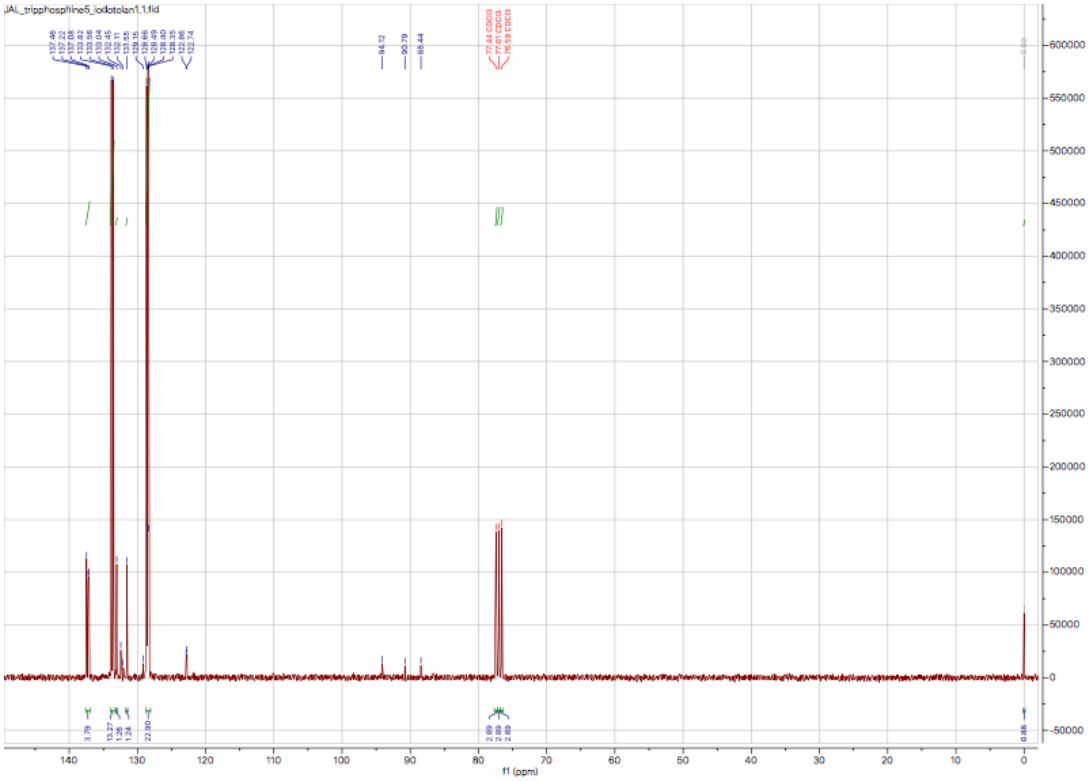

Figure 8.6: Triphenylphosphine 5:1

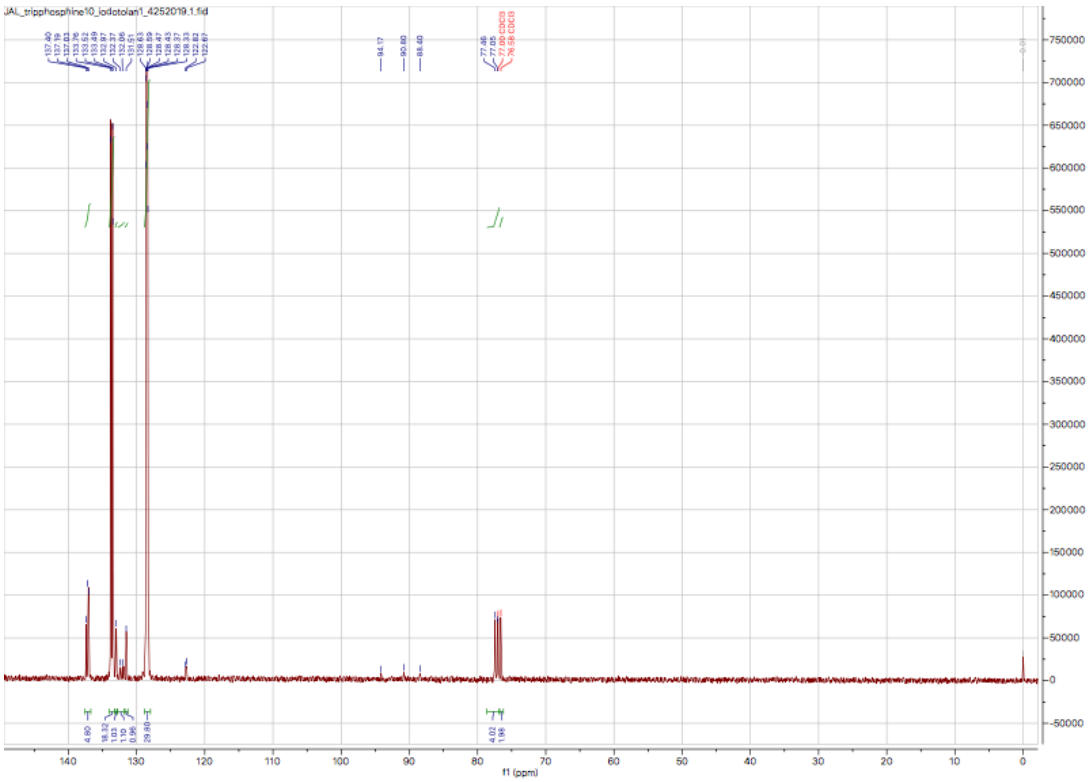

Figure 8.7: Triphenylphosphine 10:1

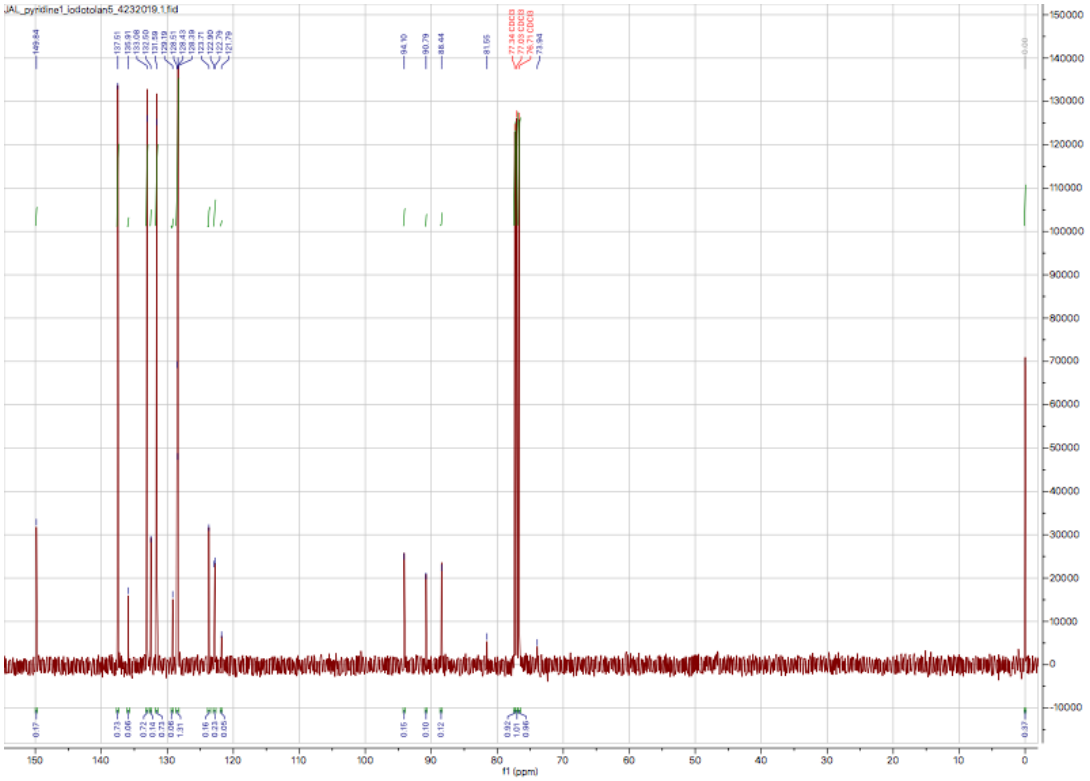

Figure 8.8: Pyridine 1:5

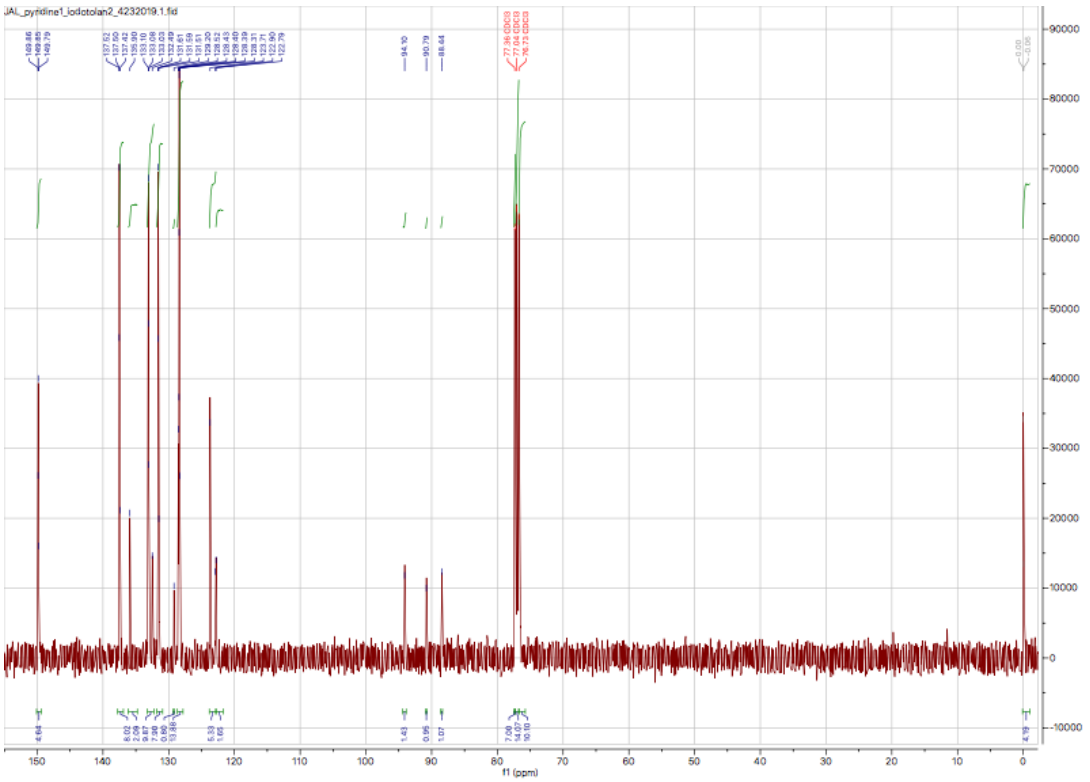

Figure 8.9: Pyridine 1:2

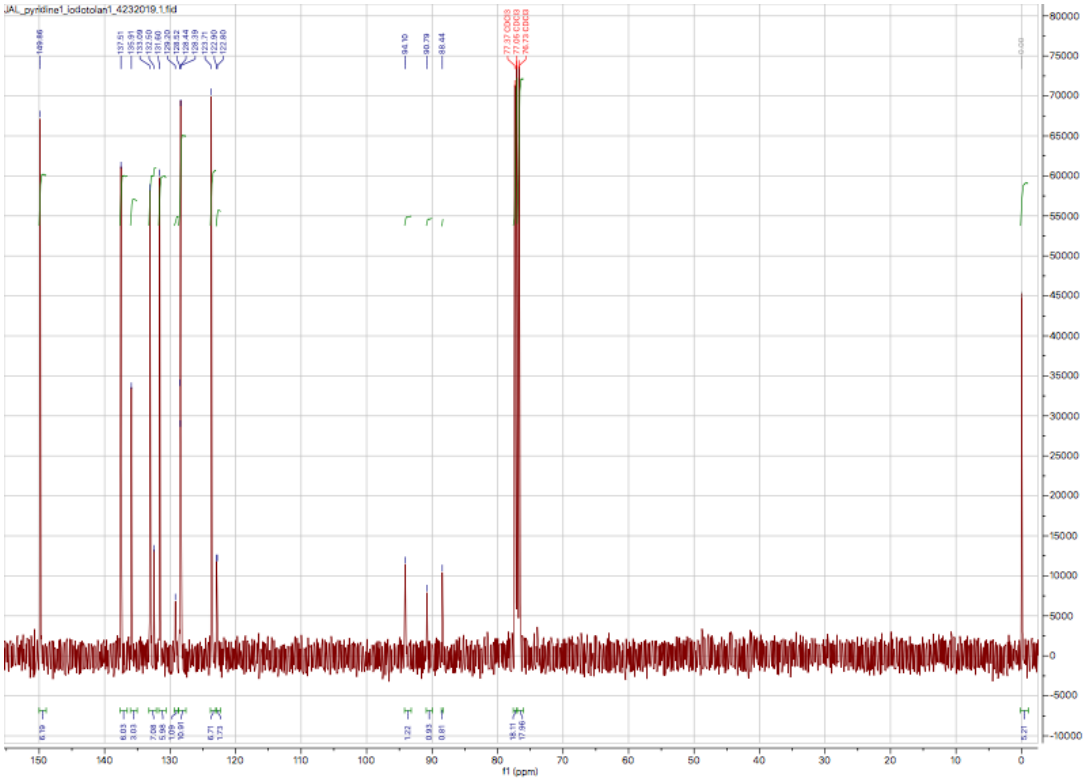

Figure 8.10: Pyridine 1:1

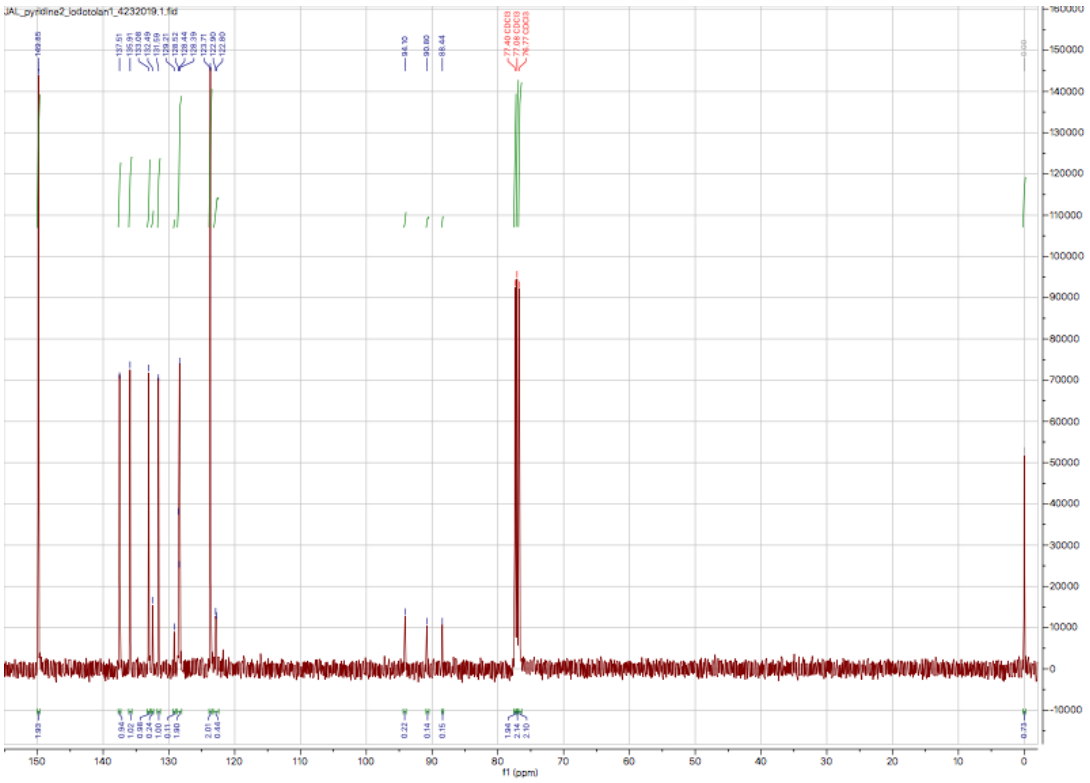

Figure 8.11: Pyridine 2:1

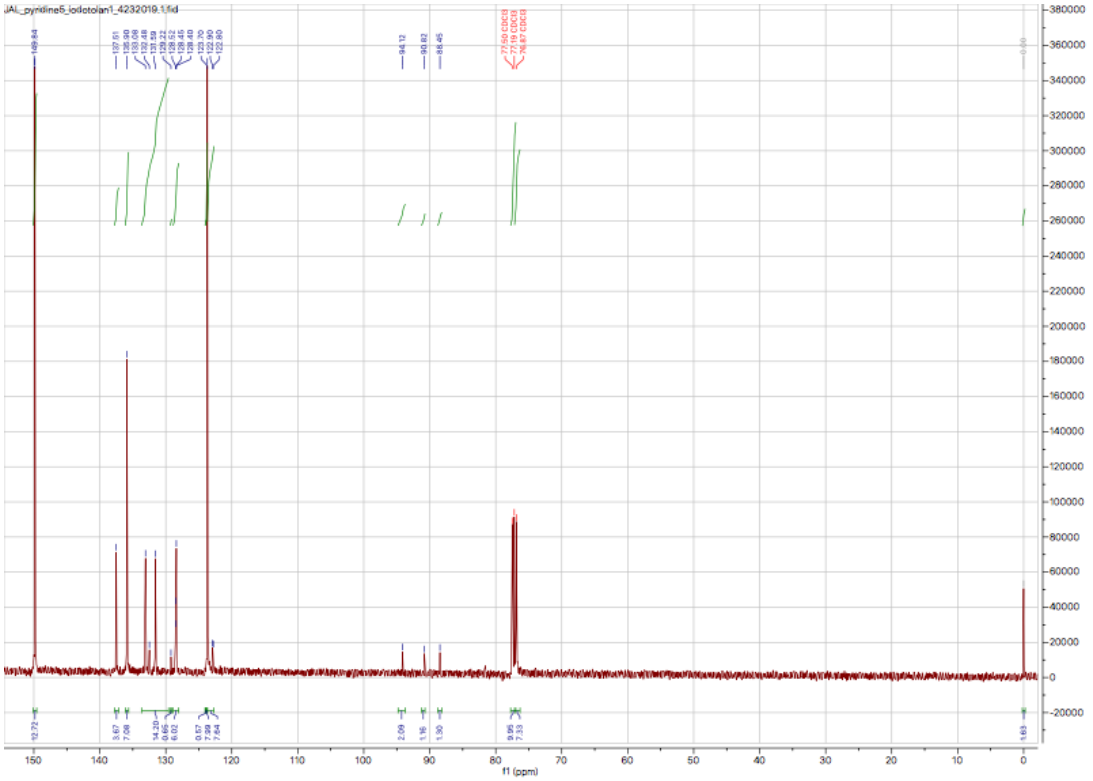

Figure 8.12: Pyridine 5:1

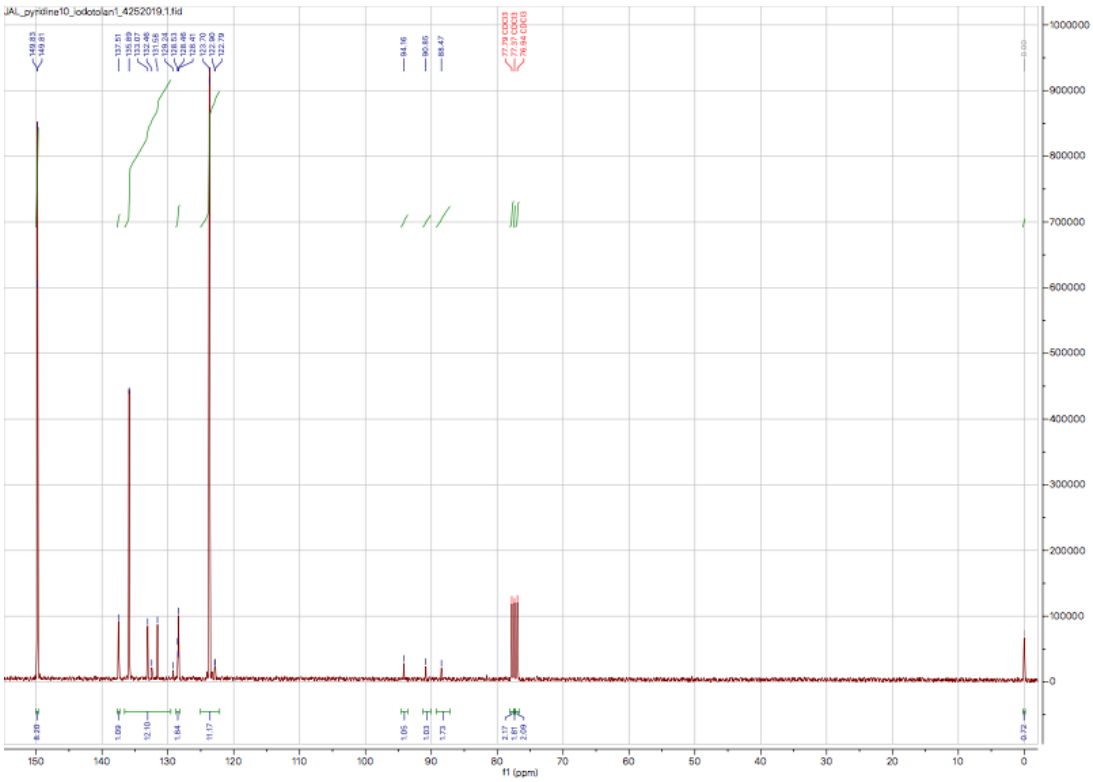

Figure 8.13: Pyridine 10:1

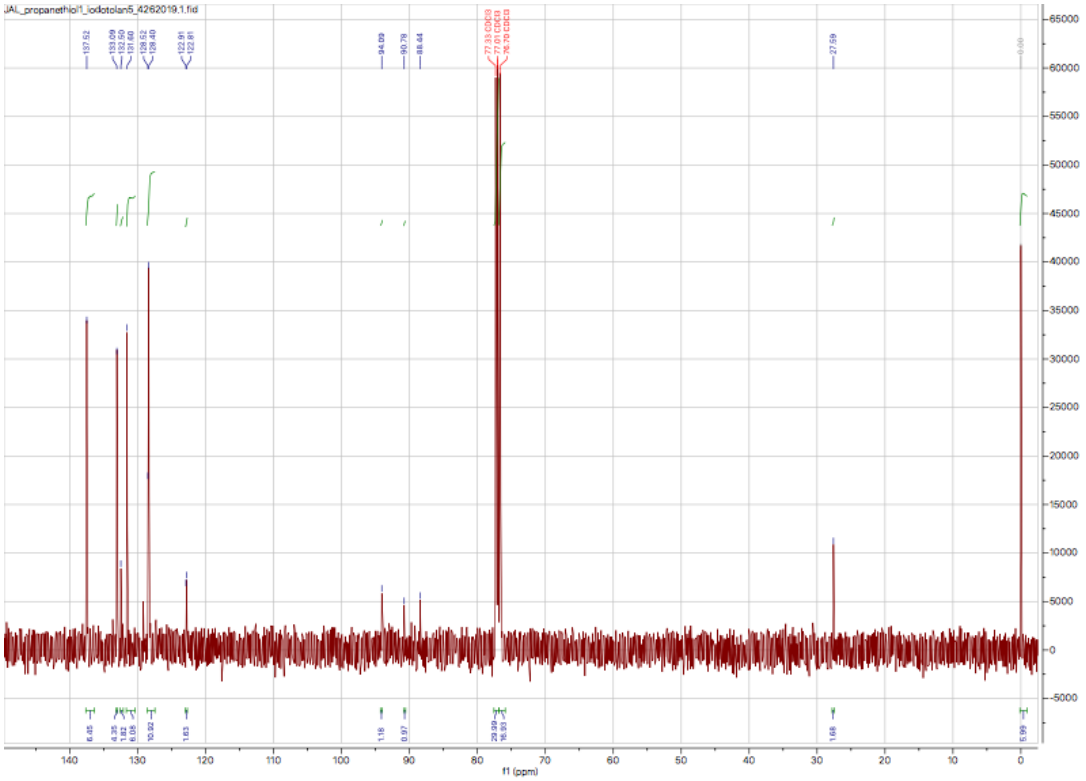

Figure 8.14: 3-Propanethiol 1:5

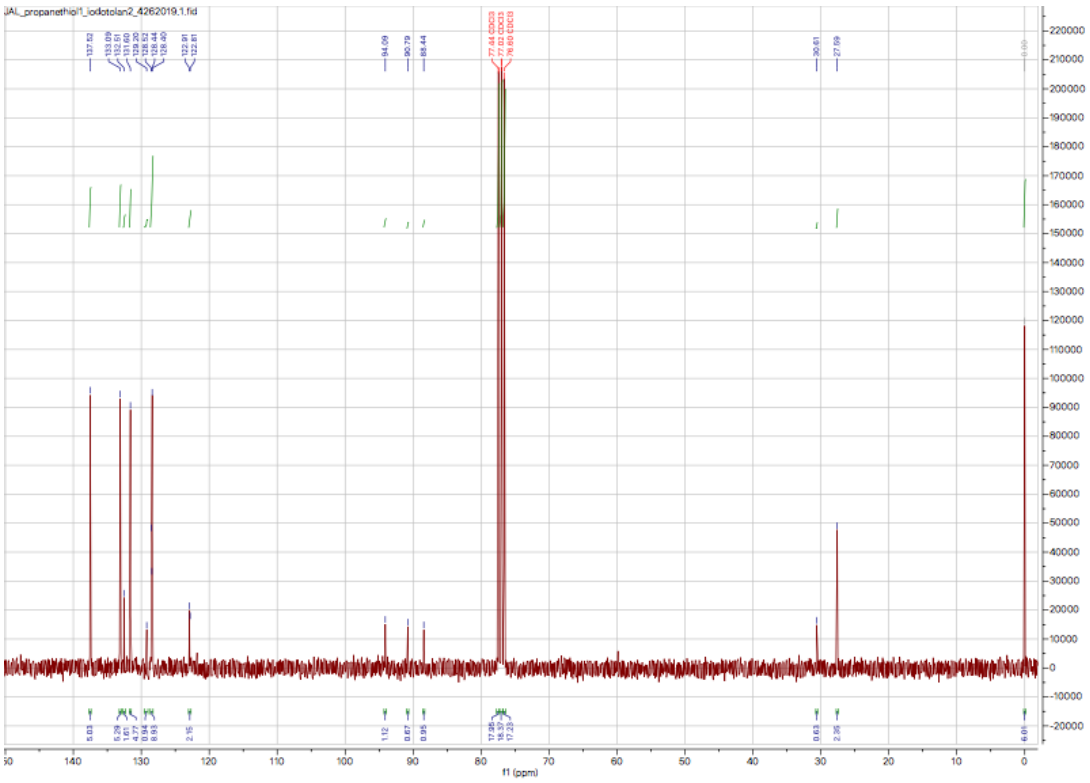

Figure 8.15: 3-Propanethiol 1:2

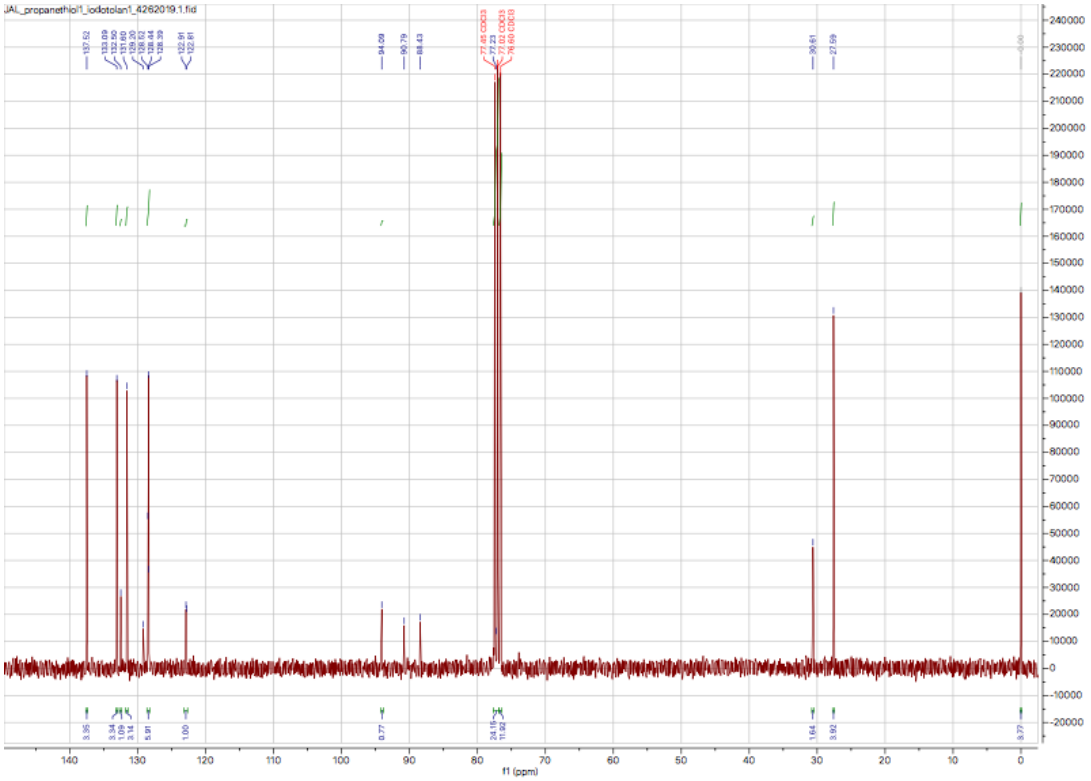

Figure 8.16: 3-Propanethiol 1:1

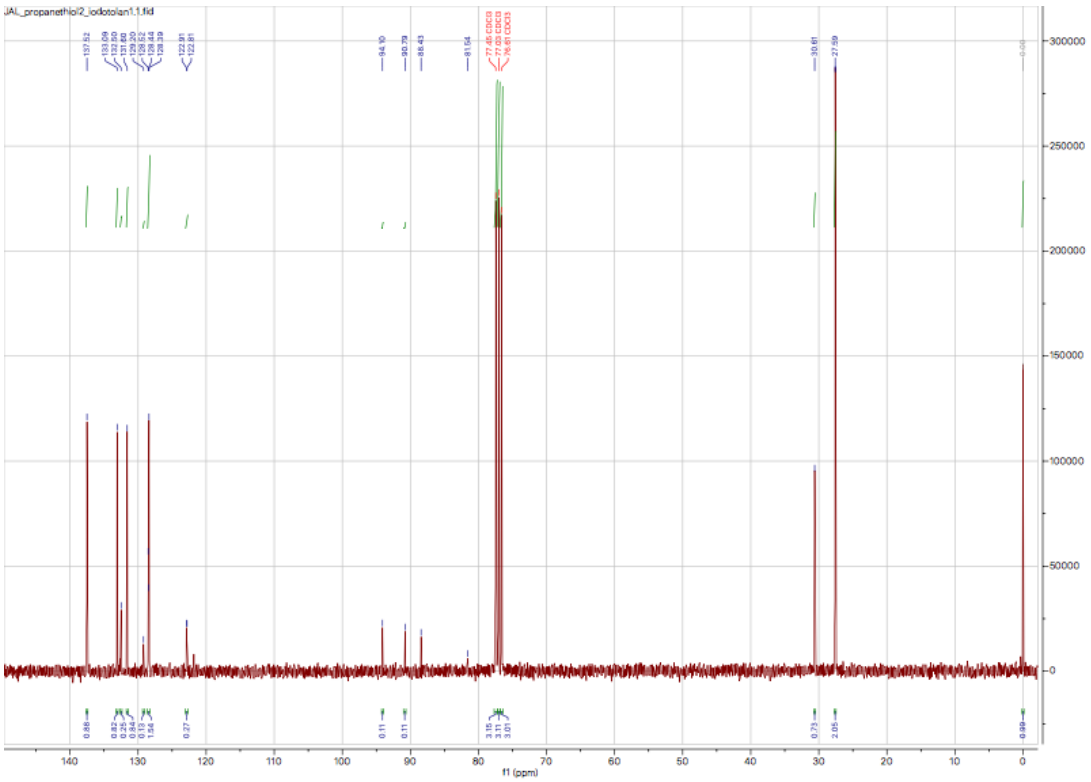

Figure 8.17: 3-Propanethiol 2:1

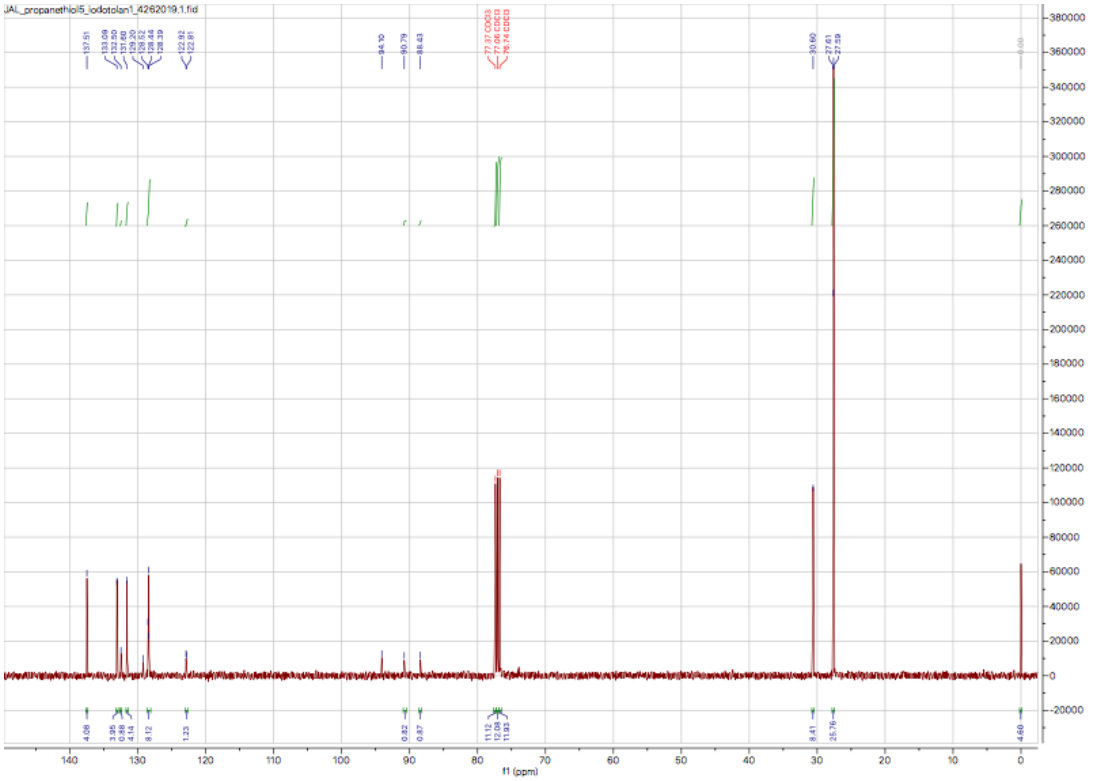

Figure 8.18: 3-Propanethiol 5:1

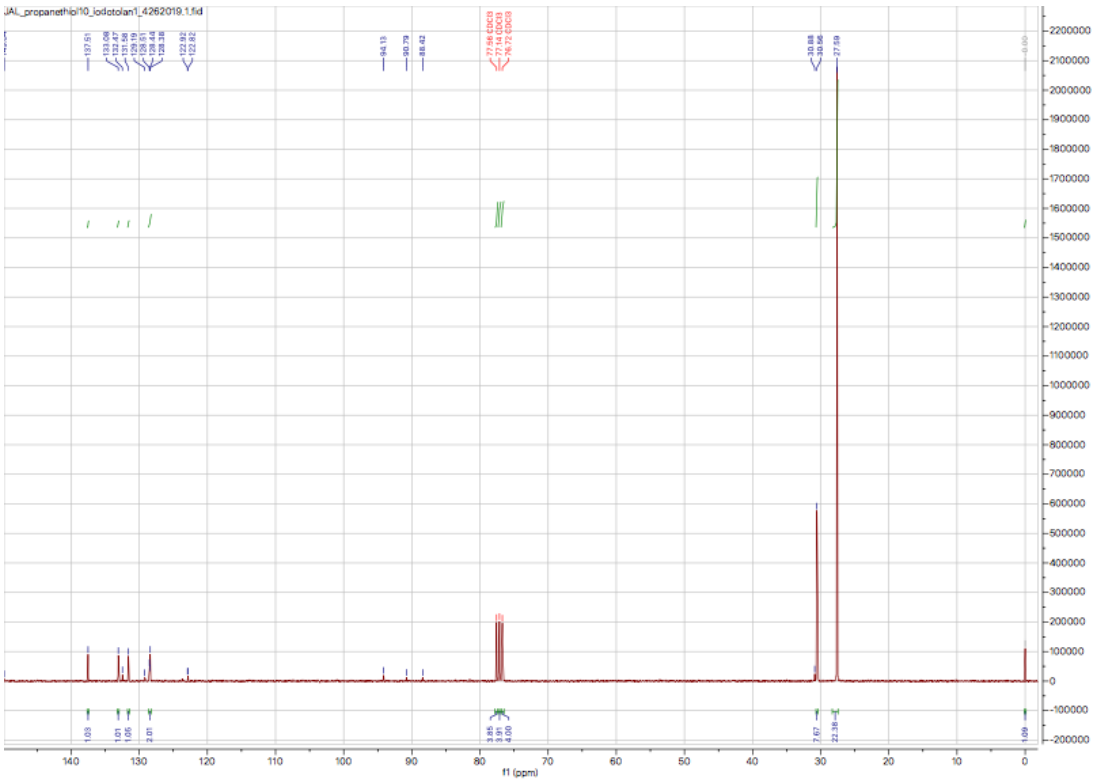

Figure 8.19: 3-Propanethiol 10:1